AR201-13318

Richard Henrich <RHENRICH@glcc.com> on 11/28/2001 06:21:49 PM

To: NCIC OPPT/DC/USEPA/US@EPA
cc:

Subject: Test Plan And Robust Summary Submission

Great Lakes Chemical Corporation (GLCC) is pleased to submit, attached below, the Test Plans and Robust Summaries for the following chemicals:

Phosphoric acid, tris(methylphenyl)ester-CAS# 1330-78-5

Phenol, isopropylated, phosphate (3:1) - CAS# 68937-41-7

GLCC is sponsoring these chemicals and submitting this information due to its acquisition of FMC's Polymer Additives product line. Great Lakes understands there will be a 120-day review period for the Test Plans and that all comments received by EPA will be forwarded to Great Lakes.

Please feel free to contact Robert Campbell (765-497-6173) or myself (765-497-6114) with any questions you might have concerning this submission.

Sincerely,

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HPVTCPTestPlan2.doc HPVIPTPPTest Plan.doc HPVTCPRobustSummary2.rtf

HPVIPTPPRobustSummary.rtf

HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

TEST PLAN

And

ROBUST SUMMARIES

For

Phosphoric acid tris(methylphenyl) ester
(Tricresyl phosphate)

CAS No. 1330-78-5

Prepared by

Great Lakes Chemical Corporation
Highway 52 N.W.
West Lafayette, IN 47996

November 28, 2001

TEST PLAN

PHOSPHORIC ACID TRIS(METHYLPHENYL) ESTER
(Tricresyl Phosphate)

CAS #1330-78-5

Study Type	Data Available	Data Acceptable	Testing Required
Physical/Chemical Characteristics			
Melting Point	NA	NA	NA
Boiling Point	Yes	Yes	No
Vapor Pressure	Yes	Yes	No
Partition Coefficient	Yes	Yes	No
Water Solubility	No	NA	Yes
Environmental Fate			
Photodegradation	No	NA	Yes
Stability in Water	No	NA	Yes
Biodegradation	Yes	Yes	No
Fugacity	No	NA	Yes
Acute Toxicity to Fish	Yes	Yes	No
Acute Toxicity to Aquatic Invert.	Yes	Yes	No
Toxicity to Aquatic Plants	No	NA	Yes
Human Health Effects			
Acute Toxicity	Yes	Yes	No
General Toxicity (Repeated Dose)	Yes	Yes	No
Genetic Toxicity	Yes	Yes	No
Reproductive Toxicity	Yes	Yes	No
Developmental Toxicity	No	NA	Yes

NA = Not Applicable

AR201-13318B

IUCLID

Data Set

Existing Chemical	:	ID: 1330-78-5
CAS No.	:	1330-78-5
EINECS No.	:	215-548-8
TSCA Name	:	Phosphoric acid, tris(methylphenyl) ester
Molecular Formula	:	C21H21O4P
Producer Related Part		
Company	:	GREAT LAKES CHEMICAL CORPORATION
Creation date	:	07.06.2001
Substance Related Part		
Company	:	GREAT LAKES CHEMICAL CORPORATION
Creation date	:	07.06.2001
Memo	:	
Printing date	:	27.07.2001
Revision date	:	
Date of last Update	:	27.07.2001
Number of Pages	:	28
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

Type	:	cooperating company
Name	:	GREAT LAKES CHEMICAL CORPORATION
Partner	:	
Date	:	
Street	:	HIGHWAY 52 N.W., P.O. Box 2200
Town	:	47996-2200 WEST LAFAYETTE, INDIANA
Country	:	United States
Phone	:	765-497-6100
Telefax	:	765-497-6234
Telex	:	27-9428
Cedex	:	
Reliability	:	(1) valid without restriction

19.07.2001

1.0.2 LOCATION OF PRODUCTION SITE

Name of Plant	:	Great Lakes Chemical Corporation
Street	:	200 Pickens Road
Town	:	25143 Nitro, West Virginia
Country	:	United States
Phone	:	304-755-6300
Telefax	:	
Telex	:	
Cedex	:	
Reliability	:	(1) valid without restriction

19.07.2001

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type	:	organic
Physical status	:	liquid
Purity	:	= 100 % w/w
Reliability	:	(1) valid without restriction

07.06.2001

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

tricresyl phosphate
07.06.2001

tritolyl phosphate
Reliability : (1) valid without restriction
07.06.2001

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

Type : industrial
Category : Basic industry: basic chemicals
07.06.2001

1.7.1 TECHNOLOGY PRODUCTION/USE

Type : Production
Reliability : (1) valid without restriction
07.06.2001

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

Memo : During production and use
Reliability : (1) valid without restriction
07.06.2001

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

Type : Handling
Remark : Avoid the generation of mists in occupied areas.
Reliability : (1) valid without restriction
07.06.2001

Type : Storage
Remark : Store in closed containers when not in use.
Reliability : (1) valid without restriction
07.06.2001

1.10.2 EMERGENCY MEASURES

Type : accidental spillage
Remark : Keep material out of streams and sewers. Absorb spilled material on commerical oil absorbant or sand. Put the contaminated absorbant into a DOT approved container.
Reliability : (1) valid without restriction
07.06.2001

Type : injury to persons (skin)
Remark : Wash with plenty of soap and water. Get medical attention if irritation occurs and persists.
07.06.2001

Type : injury to persons (eye)
Remark : Flush with water for at least 15 minutes. If irritation occurs and persists, obtain medical attention.
Reliability : (1) valid without restriction
07.06.2001

Type : injury to persons (oral)
Remark : Rinse mouth with water. Dilute by giving one or two glasses of water. Never give anything by mouth to an unconscious person. See a medical doctor immediately.
Reliability : (1) valid without restriction
07.06.2001

Type : injury to persons (inhalation)
Remark : Remove to fresh air. If breathing difficulty or discomfort occurs and persists, contact a medical doctor.
Reliability : (1) valid without restriction
07.06.2001

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

Memo : Any amount not used should be disposed of according to all applicable regulations.
Reliability : (1) valid without restriction
07.06.2001

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

Type : TSCA
Additional info :
Reliability : (1) valid without restriction
07.06.2001

2.1 MELTING POINT

2.2 BOILING POINT

Value	:	= 241 - 255 ° C at .533 hPa
Decomposition	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable

19.07.2001

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .0044 hPa at 150° C
Reliability	:	(4) not assignable

19.07.2001

2.5 PARTITION COEFFICIENT

Log pow	:	= 5.93 at ° C
Method		
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable

27.07.2001 (8)

2.6.1 WATER SOLUBILITY

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	= 225 ° C
Type	:	closed cup
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable

19.07.2001

2.8 AUTO FLAMMABILITY

Value : = 607 ° C at
Reliability : (4) not assignable
19.07.2001

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge, domestic
Contact time	:	24 hour(s)
Degradation	:	= 70 - 80 % after 24 hour(s)
Result	:	
Deg. Product	:	
Method	:	
Year	:	1982
GLP	:	no
Test substance	:	other TS: tri-p-cresyl phosphate
Method	:	The biodegradation of tri-p-cresyl phosphate was determined in sewage sludge, over a 24 hour period. 14C-TPCP was added to the model sewage sludge system in the amount of 1 ug/ml, and the incubation was maintained at room temperature (21 degrees C). The percent TPCP degraded was determined by liquid scintillation counting, gas chromatography, and thin layer chromatography. Metabolites were isolated and identified when possible.
Result	:	At the end of the 24 hour incubation, 70 to 80% of the TPCP was degraded. The remaining TPCP was associated with sludge solids. The major metabolite extracted from the sludge by ethyl ether was identified as p-hydroxybenzoic acid. Two unstable ether-extractable metabolites were not identified. The half-life of TPCP was determined to be 7.5 hours.
Reliability 20.06.2001	:	(2) valid with restrictions

(16)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	m = 56
LC50	:	m > 100
Method	:	
Year	:	1978
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Five dosage groups, each consisting of 10 flathead minnows, were exposed under static conditions to TCP for up to 96 hours. The water as at pH 7.23, hardness of 44 mg/l, and total alkalinity of 32 mg/l. Nominal exposure concentrations of TCP were 10, 18, 32, 56, and 100 mg/l.
Result	:	Mortality occurred only in the 100 mg/l group, with 20% of the test population (2 of 10 fish) dying at 72 hours. The 96 hour LC50 is >100 mg/l.
Reliability	:	(2) valid with restrictions

20.06.2001 (31)

Type	:	static
Species	:	Salmo gairdneri (Fish, estuary, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	m < .56
LC50	:	m = .75
Method	:	other: Committe on Methods for Toxicity Tests with Aquatic Organisms
Year	:	1978
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Ten rainbow trout were used for each of five dosage groups. The fish were place in water at pH 7.4, total hardness of 42 mg/l, and total alkalinity of 30 mg/l. Exposure levels were 0.56, 1.00, 1.80, 3.20, and 5.60 mg/l, provided as nominal concentrations. Mortality was measured at 24, 48, 72, and 96 hours.
Result	:	The 96 hour LC50 was determined as 0.75 mg/l with 95% confidence limits of 0.54 to 1.04 mg/l. There was no mortality in the solvent control. Mortality occurred in all treatment groups. An NOAEC was not identified experimentally in this test.

20.06.2001 (29)

20.06.2001

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	m = .1
EC50	:	m = .27
Method	:	
Year	:	1979

GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Five organisms were used in each test chamber. The test contained three replicates of each nominal concentration, 4 control replicates, and 4 solvent control replicates. The solvent used was acetone (200 ml per chamber). Nominal concentrations of TCP were 0.06, 0.10, 0.18, 0.32, and 0.56 mg/l. A NOAEL level and an LC50 level were determined at 96 hours.
Result	:	There was no mortality in the 0.06 and 0.10 mg/l TCP groups or in the control groups. Mortality occurred in a dose-response manner in the three highest dose groups. The 48 hour LC50 concentration (nominal) was determined to to 0.27 mg/kg, with 95% confidence limits of 0.21 to 0.33 mg/l.
Reliability	:	(2) valid with restrictions

20.06.2001 (30)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

Method	:	The absorption, distribution, and elimination of a single dose of tri-ortho-cresyl phosphate (TOCP, the ortho isomer of TCP) was evaluated in adult While Leghorn hens. Uniformly ring labeled 14C-TOCP was administered at a dose of 50 mg in a capsule to 12 hens which were then housed in metabolism cages. Excreta was collected daily for up to 5 days. Three control hens were included in the study. Blood was collected via heart puncture just prior to sacrifice. Three treated hens were terminated at 0.5, 1, 2, and 5 days. Tissue distribution of the radioactivity was determined in all of the animals. TOCP and metabolites were extracted with ethyl acetate and identified using HPLC and reference standards.
Result	:	Hens that received the 50 mg doses did not express either acute cholinergic signs or symptoms of delayed neurotoxicity. TOCP was absorbed from the gastrointestinal tract, with highest concentrations appearing in the bile, kidneys, liver, and lungs. About 47% of the radioactivity was excreted in the first 12 hours. About 99% was eliminated

after 5 days. HPLC identified TOCP and nine metabolites. The active metabolite, saligenin cyclic-o-cresyl phosphate, was the predominent compound found in the excreta. The relatively slow excretion of TOCP and its metabolites by the hen may contribute to its sensitivity as an animal model in the study of delayed neurotoxicity.

Reliability : (2) valid with restrictions
19.07.2001 (1)

Method : The disposition of 10 daily doses of 14C-tri-ortho-cresyl phosphate (TOCP), 50 mg/kg, was determined in male Fischer 344 rats. Groups of 3 rats each were sacrificed at 24, 48, 72, and 96 hours after the last dose. The distribution of radioactivity in 19 tissues was measured. Urine and feces were collected up to time of sacrifice. TOCP and its metabolites were analyzed and quantified by HPLC using appropriate reference standards.

Result : The highest concentrations of radioactivity were found in the liver, adipose tissue, epididymis, sciatic nerve, plasma, and erythrocytes. Lowest concentrations were in the testes, brain, spleen and heart. All radioactivity had been excreted 4 days after the last dose. Analysis of the radioactivity in several tissues showed TOCP to be the predominent compound present. The major metabolites were identified.

Reliability : (2) valid with restrictions
19.07.2001 (26)

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: none
Value	:	> 20000 mg/kg bw
Method	:	EPA OTS 798.1175
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Five male and 5 female Wistar rats received a single 20,000 mg/kg oral dose of TCP by gavage. The animals were then held and observed 14 days.
Result	:	Two of 5 male rats and 2 of 5 female rats died on days 3 and 7, respectively, during the 14 day observation period. Therefore, the acute oral LD50 is greater than 20,000 mg/kg.
Reliability	:	(1) valid without restriction

18.06.2001 (11)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Exposure time	:	1 hour(s)
Value	:	< 200 mg/l
Method	:	other
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Five male and 5 female Wistar rats were placed in a glass chamber into which TCP was introduced at a nominal concentration of 200 mg/liter. The animals were removed from the chamber after a 1 hour exposure and were observed for 14 days.
Reliability	:	(3) invalid The nominal chamber concentration reported of 200 mg/l cannot be achieved. No information is provided as to the type of inhalation chamber used, the method of TCP aerosolization, the particle size achieved (respirable?), or other data that are essential to determining the validity of a study.

18.06.2001 (7) (10)

Type	:	LC50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	20
Vehicle	:	
Exposure time	:	4 hour(s)
Value	:	> 5.2 mg/l
Method	:	EPA OTS 798.1150

Year	:	1979
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of 10 male and 10 female rats were exposed to a fine aerosol of test substance at a measured mean concentration of 5.2 mg/l for 4 hours. Aerosol particle size remained in the 3.0 to 3.1 um MMAD and inhalation chamber exposure parameters were maintained within desired limits throughout the exposure period.
Result	:	No mortality was observed in either sex during the 14 day observation period. Immediately after exposure, toxic signs included depression and ruffled fur. All animals appeared normal on day 2. Mean body weights for the treated male and female rats at the end of the observation period were no different than control body weights. At necropsy, red and/or brown focu were seen on the lungs of 5 of the 20 exposed rats. The results of this study indicate that the acute inhalation LC50 is greater than 5.2 mg/l.
Reliability	:	(1) valid without restriction

20.06.2001 (27)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	10
Vehicle	:	other: none
Value	:	> 10000 mg/kg bw
Method	:	EPA OTS 798.1100
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	TCP was applied to the shaved backs of 10 albino rabbits at a dose of 10,000 mg/kg. Five of the application sites were intact while the other 5 sites were abraded. The animals were observed daily for 14 days for signs of toxicity.
Result	:	There was no mortality in this study. No clinical signs of toxicity were reported. Therefore that acute dermal toxicity of TCP is greater than 10,000 mg/kg.
Reliability	:	(1) valid without restriction

18.06.2001 (9)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	100 %
Exposure	:	Semiocclusive
Exposure time	:	24 hour(s)
Number of animals	:	6
PDII	:	
Result	:	not irritating
EC classification	:	not irritating
Method	:	Draize Test
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	The backs of six albino rabbits were shaved 24 hours prior to treatment. The TCP was applied to the intact left side of the back and the abraded right side of the back. The areas were wrapped in surgical gauze for 24 hours, after which the gauze was removed and the skin was observed for irritation.
Result	:	Erythema was observed in the abraided skin of one animal at 24 hours. The erythema was gone at the 72 hour observation. None of the animals showed edema at either the abraded or unabraded (intact) application areas. Thus TCP did not cause skin irritation in this test.
Reliability	:	(1) valid without restriction

18.06.2001 (13)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	100 %
Dose	:	.1 ml
Exposure Time	:	
Comment	:	
Number of animals	:	9
Result	:	not irritating
EC classification	:	not irritating
Method	:	Draize Test
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The right eye of 9 rabbits received 0.1 ml of undiluted TCP. The eyes of 6 rabbits remained unwashed during the observation period whil the eyes of 3 rabbits were washed 4 seconds after application. All eyes were examined at 24, 48, and 72 hours after exposure, and again after 7 days. The eyes were scored according to the method of Draize.
Result	:	Conjuctival effects were observed at 24 hours in two of the six rabbits with unwashed eyes, which cleared by 48 hours. No ocular effects were observed in the eyes of rabbits whose eyes were washed 4 seconds after application. The laboratory reports that, on the basis of these results, TCP is not an eye irritant.
Reliability	:	(1) valid without restriction

18.06.2001 (12)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	0.1, 0.5, and 1.0% of diet
Control group	:	yes, concurrent no treatment
NOAEL	:	= .1 %
LOAEL	:	= .5 %
Method	:	other
Year	:	1976

GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of Sprague Dawley rats consisting of 10 male and 10 female animals each received dietary doses of either 0, 0.1, 0.5, or 1.0% of the diet, daily for 28 days. All animals were examined daily for appearance and signs of toxicity. Body weights were determined at the start of the study and weekly thereafter. After the 28 day exposure, blood and urine samples were collected from each animal. Then, the animals were sacrificed, necropsied, and underwent gross examination. The following organs were weighed: brain, thyroid, heart, liver, spleen, testes, ovaries, and kidneys. Representative samples of tissues were retained in 10% neutral formalin for possible histopathological examination. The blood samples were used for hematological evaluation (hemoglobin, hematocrit, erythrocyte count, total and differential leukocyte count) and for measuring several clinical chemistry parameters. Urinalysis included pH, glucose, ketones, bilirubin, and occult blood.
Result	:	All 10 male and 9 of 10 female rats that received the 1.0% diet died. Four males and five females from the 0.5% dose group died during the study. Only one male rat died in the low dose group. Animals in the mid dose group had significantly lower body weights and food consumption when compared to the control animals. Mortalitity occurred too quickly in the high dose group to develop meaningful body weight or food consumption data. There was no effect on either parameter in the low dose group. Hematological and urinalysis values were not affected by treatment. BUN and cholesterol levels were elevated in the mid dose animals. No gross lesions were observed that were considered treatment related. In evaluating organ to body weight ratios, only the liver to body weight ratio was increased, and only in the mid dose group. The 0.1% dietary level is considered the NOAEL.
Reliability	:	(2) valid with restrictions
19.06.2001		(14)

Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	gavage
Exposure period	:	20, 40, and 60 days
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	0.4 g/kg/day in sesame oil
Control group	:	yes, concurrent vehicle
Method	:	other: special design
Year	:	1994
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 3 male and 3 female Fischer 344 rats received daily doses of 0.4 g/kg TCP by oral gavage for either 20, 40, or 60 days. Rats were weighed weekly. At termination, the adrenal glands, ovaries, testes, and epididymides were removed, placed in either 10% formalin (adrenals and ovaries) or Bouin's fixative (testes and epididymides), and prepared for microscopic examination. Both light and electron microscopy were used to examine the tissues.
Result	:	Since only one dose level was used in the study, dose-response data were unattainable. Diagnostic pathology revealed hypertrophy and cholesteryl lipidosis of adrenocortical (both sexes) and ovarian interstitial cells that were progressive with duration of treatment. Decreased testicular weights and degeneration of the seminiferous tubules were detected in all 9 of the male rats.
Reliability	:	(2) valid with restrictions
20.06.2001		(18)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	three months
Frequency of treatment	:	daily, six days per week, for 3 months
Post obs. period	:	
Doses	:	30, 100, 300, and 1000 mg/kg/day
Control group	:	yes, concurrent vehicle
Method	:	
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of Sprague-Dawley rats, each consisting of 5 male and 5 female animals, received daily gavage doses of TCP, 6 days per week, for 3 months. The vehicle control animals received a 5% gum arabic solution, which was used to prepared dosing solutions of TCP. Animals were observed daily for clinical signs and their body weights and food consumption measured weekly. Urinalysis (ph, sugar, protein, ketone bodies, blood) was performed monthly and hematological evaluations (hemoglobin, hematocrit, erythrocyte and leucocyte counts, packed cell volume) were conducted at the end of the in-life phase of the study. Clinical chemistry assessments, including glucose, albumin, BUN, alkaline phosphatase, SGOT, total protein, and electrolytes levels, were also performed at the end of 3 months exposure. All animals were necropsied with organs undergoing gross examination. Organs, including the liver, kidney, spleen, heart, lungs, brain, spinal cord, and urinary bladder, were processed through histology for diagnostic pathology.
Result	:	Other than excessive salivation in a few animals in all doses shortly after gavage administration of TCP, there were no clinical signs suggestive of systemic toxicity. There was no TCP induced mortality. One animal died in the 30 mg/kg group from handling error. A significant decrease in body weight gain was observed in the high dose male rats throughout the test. No treatment-related changes were observed in the urinalysis or in the hematological assessment. The clinical chemistry evaluation of serum revealed a decrease in albumin levels and an increase in potassium levels in the 300 mg/kg male and female rats. No significant changes were seen in serum enzyme activities. All treatment groups showed a slight increase in liver weights. An increase in adrenal gland weight was seen in the 1000 mg/kg females and a slight decrease in spleen, heart, and lung weights i n the high dose males. The only treatment-related morphologic change observed in any group was hypertrophy of the adrenal cortex in the 1000 mg/kg group.
Reliability	:	(2) valid with restrictions

20.06.2001 (28)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Cytogenetic assay
System of testing	:	Mouse Lymphoma Cell Line for Chromosomal Aberrations and Sister Chromatid Exchanges
Concentration	:	0.00063, 0.00125, 0.00250, 0.0050, and 0.010 ul/ml
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	EPA OTS 798.5375
Year	:	1979
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Reliability	:	(1) valid without restriction
20.06.2001		(20)
Type	:	Mouse lymphoma assay
System of testing	:	Mouse Lymphoma L5178Y Cells
Concentration	:	0.488, 7.8, 15.6, 31.8, 40, and 62 nl/ml
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	ambiguous
Method	:	EPA OTS 798.5300
Year	:	1979
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
20.06.2001		(22)
Type	:	Salmonella typhimurium reverse mutation assay
System of testing	:	Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100
Concentration	:	0.1 microliter of 100, 10, 1, 0.1 and 0.01% TCP solutions
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	EPA OTS 798.5265
Year	:	1977
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(1) valid without restriction
18.06.2001		
Type	:	Salmonella typhimurium reverse mutation assay
System of testing	:	Salmonella typhimurium testor strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100
Concentration	:	0.005, 0.01, 0.1, 1.0, 5.0, and 10.0 ul per plate
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	EPA OTS 798.5265
Year	:	1979
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(1) valid without restriction
20.06.2001		(21)
Type	:	other
System of testing	:	BALB/3T3 Cell Line
Concentration	:	0.000156, 0.00125, 0.010, 0.02, 0.04 ul/ml
Cycotoxic conc.	:	
Metabolic activation	:	without
Result	:	positive
Method	:	EPA OTS 795.2850
Year	:	1979
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(1) valid without restriction
20.06.2001		(19)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENITY

Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	Two Years
Frequency of treatment	:	Daily
Post. obs. period	:	
Doses	:	0, 75, 150, 300 ppm
Result	:	negative
Control group	:	yes, concurrent no treatment
Method	:	EPA OTS 798.3320
Year	:	1994
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups consisting of 95 male and 95 female F344 rats received tricresyl phosphate (TCP) in their diets at levels of 75, 150, or 300 ppm for 105 weeks. A concurrent control group received just diet. Dose selection was based on results from a 13 week feeding study, which included lower mean body weights, toxic responses to the kidney, pituitary, and testes at a dose of 6600 ppm, and cytoplasmic vacuolization of the adrenal cortex at doses of 900 and 1700 ppm. All animals were observed twice daily for clinical signs and mortality. Neurobehavioral assessments were performed before initial exposure and just prior to necropsy at the 3, 9, and 15 month interim sacrifices. Hematology and clinical chemistry parameters were measured at each interim sacrifice, and the right adrenal gland, right testes, right kidney, and liver was removed at the interim sacrifices. At the interm and terminal sacrifices, necropsies were performed on all animals, organs and tissues were removed and fixed in formalin, embedded in parafin, sectioned, stained, and examined microscopically for treatment-related abnormal morphology (target organ toxicity and an increase in the incidence of tumors). Hematology and clinical chemistry parameters were evaluated in the animals sacrificed after 24 months. Up to five animals per dose group were selected for special neuropathology. The brain, spinal cord, and sciatic nerve were removed, placed in formalin, and stained with special stains (i.e., Bodian's stain, luxol fast blue) in addition to H & E.
Result	:	Survival of the treated animals was similar to that of the control animals. Mean body weights and food consumption of the exposed rats from all treatment groups were similar to the control rats throughout the study. No clinical signs were noted that were attributable to treatment. There were no treatment-related effects on hematology or clinical chemistry parameters at the time of interm sacrifice or at the study termination, except for certain cholinesterase values. Serum cholinesterase activity, but not brain or erythrocyte cholinesterase activity, was decreased in the 300 ppm animals at the interim sacrifices, but not at study termination. Throughout the study, the incidence of cytoplasmic vacuolization of the adrenal cortex and interstitial cell hyperplasia of the ovaries were significantly increased in the 300 ppm animals. In the special neurological assessment, no abnormal changes in the brain, spinal cord, or sciatic nerve was observed. However, hindlimb grip strength was lower than controls in the high dose animals at interm sacrifices, but not at the terminal sacrifice. Ingestion of TCP for up to two years did not increase the incidence of tumors in any tissue. Thus, there was no evidence of carcinogenic activity in the male and female rats.
Reliability 18.06.2001	:	(1) valid without restriction

(24)

Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	Two Years
Frequency of treatment	:	Daily
Post. obs. period	:	
Doses	:	60, 125, or 250 ppm
Result	:	negative
Control group	:	yes, concurrent no treatment
Method	:	EPA OTS 798.3320
Year	:	1994
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 95 male and 95 female mice received either 0, 60, 125, or 250 ppm tricresyl phosphate (TCP) in their diet for up to two years. Dose selection was based on 13 week feeding study in mice, in which the dose of 1000 ppm caused axonal degeneration and the dose of 500 ppm caused cytoplasmic vacuolization of the adrenal cortex. All animals were observed twice daily for clinical signs of toxicity. Body weights, food consumption and survival were recorded at specified intervals. Interim sacrifices occurred after 3, 9, and 15 months of exposure, at which time the mice were evaluated for hindlimb grip strength and for histopathologic lesions. At 24 months, the remaining animals were sacricied, necropsied, and certain organs weighed. All tissues/organs were removed and processed for diagnostic pathology.
Result	:	Survival of TCP treated male and female mice were similar to that of the control animals. Food consumption by the male and female mice that ingested TCP for up to 24 months was similar to that by the control mice. Dietary levels of 60, 125, or 250 ppm were estimated to deliver average daily doses of 7, 13, or 27 mg/kg body weight (males) and 8, 18, or or 37 mg/kg (females). There were no biologically significant differences in hematology parameters at interim or final evaluations. There were dose-related decreases in serum cholinesterase activity in all groups of exposed mice at the 3, 9, and 15 month evaluations. Hindlimb grip strength in 250 ppm female mice was significantly lower than in the controls at the 3 month interim evaluation. At the 9 and 15 month evaluations, the grip strength of the exposed male and female mice was similar to that of the control animals. Diagnostic pathology revealed an increase in the severity of ceroid pigmentation in the adrenal cortex in most of the exposed groups (males and females) at the 9 month interim evaluation. At 15 months, there was a dose-related increase in ceroid pigmentation of the adrenal cortex in female mice. At the end of the study, a dose related increase in ceroid pigmentation was observed in the adrenal cortex and in the livers both control and exposed male and female mice. Clear cell foci and fatty changes were observed in the livers of male mice that received doses of 125 or 250 ppm. There was no increase in the incidence of either benign or malignant tumors in any organ or tissue in any of the treatment groups. Therefore, treatment with TCP for up to two years did not induce carcinogenicity in the mice in this study.
Reliability	:	(1) valid without restriction

18.06.2001 (23)

5.8 TOXICITY TO REPRODUCTION

Type	:	One generation study

Species	:	rat
Sex	:	male/female
Strain	:	Long-Evans
Route of admin.	:	gavage
Exposure period	:	
Frequency of treatment	:	daily
Premating exposure period		
Male	:	56 days
Female	:	14 days
Duration of test	:	
Doses	:	males: 100 or 200 mg/kg; females: 200 or 400 mg/kg
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1987
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The reproductive effects of tricresyl phosphate (TCP) were examined in male and female Long-Evans rats. Twelve male rats per group received doses of either 100 or 200 mg/kg/day of TCP in corn oil, for 56 days prior to breeding. Twenty-four female rats per group received either 200 or 400 mg/kg/day for 14 days prior to breeding. Animals continued to receive their respective dose during the 10 day breeding period. The 100 mg/kg males were mated with the 200 mg/kg females and the 200 mg/kg males were mated with the 400 mg/kg females. Following breeding, the males were terminated, necropsied, and several sperm parameters were evaluated. The reproductive tract underwent histopathological examination. females were dosed through gestation and lactation. Pups and adult females were then necropsied on postnatal day 21.
Result	:	Sperm concentration, motility, and progressive movement were decreased in the male rats that received 200mg/kg/day. A dose-dependent increase in abnormal sperm morphology was observed in the males from both treatment groups. The number of female rats delivering live pups was severely decreased by TCP exposure. Litter size and pup viability were decreased in the 400 mg/kg/day dose group. Pup body weight and developmental parameters were unaffected by TCP exposure. Significant histopathological changes were observed in the testes and epididymides of male rats and in the ovaries of female rats exposed to TCP. There was no NOAEL in this study.
Reliability	:	(2) valid with restrictions

19.06.2001 (4)

Type	:	other: Modified Continuous Breeding Protocol
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	gavage
Exposure period	:	135 days
Frequency of treatment	:	daily
Premating exposure period		
Male	:	7 days
Female	:	7 days
Duration of test	:	
Doses	:	0.4 g/l
Control group	:	yes, concurrent vehicle
Method	:	
Year	:	1994
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	This study consisted of a naive control group (20 breeding pairs), a vehicle control group (40 breeding pairs), and a 0.4 g/kg TCP group (20 breeding pairs). The vehicle used in the study is sesame oil, administered at 1.5 ml/day. The rats were dosed for7 days prior to being paired, and then dosed for a 63 day breeding period, and then through a 28 day postbreeding interval. A crossover mating occurred between treated and control rats just after the postbreeding phase to determine which sex was affected by treatment. Fertility index, number of litters per fertile pair, and other reproductive parameters were measured.
Result	:	Repeated oral exposure to 0.4 g/kg of TCP resulted in a significant decrease in fertility index, and number of litters per fertile pair. The number of live pups per litter was also decreased in the TCP groups when compared to the control groups. In the crossover phase, there was no effect on the reproductive efficiency of the TCP treated female rats while TCP treated male rats produced no litters. These male rats had significantly decreased testicular and epididymal weights. Since only one dose was used, an NOEL was not established.
Reliability	:	(2) valid with restrictions
20.06.2001		(17)

Type	:	other: In vitro Sertoli and Leydig cell toxicity study
Species	:	rat
Sex	:	male
Strain	:	Sprague-Dawley
Route of admin.	:	other: in vitro cell exposure
Exposure period	:	
Frequency of treatment	:	
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
Doses	:	
Control group	:	
Method	:	Since both Leydig cells and Sertoli cells in the testes have been previously shown to be adversely affected by exposure to tri-ortho-cresyl phosphate (TOCP), an in vitro study was conducted to determine whether Leydig cells can activate TOCP via metabolism to the active saligenin cyclic metabolite, and whether this meabolite can adversely affect Sertoli cells in culture.
Result	:	Cultured Leydig cells were shown to meatolize TOCP to the active cyclic metabolite. TOCP decreased testosterone secretion from Leydig cells. Sertoli cells apparently cannot activate TOCP. When both cell types are co-cultured, the Leydig cell activates TOCP to the saligenin cyclic metabolite which then inhibits neurotoxic esterase in the Sertoli cells. These data indicate that TOCP can be activated directly by the testes and this may explain the target organ toxicity of TOCP to the testes.
Reliability	:	(2) valid with restrictions
19.06.2001		(6)

Type	:	other: continuous breeding protocol
Species	:	mouse
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	oral feed
Exposure period	:	Throughout 98 day continuous breeding period and through crossover mating
Frequency of treatment	:	Daily
Premating exposure period		
Male	:	

Female	:	
Duration of test	:	
Doses	:	0.05, 0.1, and 0.2% of diet
Control group	:	yes, concurrent no treatment
Method	:	other: continuous breeding protocol
Year	:	1988
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The study design consisted of using a control group of 40 breeding pairs and three dose groups each consisting of 20 breeding pairs. Doses used were based on the results of a rangefinding study, and the highest dose was chosen so as not to depress body weight gain by more than 10%. Doses were 0.0, 0.05, 0.1, and 0.2% TCP by weight in the diet. The animals were housed as breeding pairs for 98 days, following 7 days of premating consumption of dosed diet. Endpoints determined include clinical signs, body weight, fertility, litters per pair, live pups per litter, sex of live pups, and pup body weights. At the concusion of this phase of the study, a crossover breeding study was conducted in which control males were mated with treated females, and control females were mated with treated males. During this phase, the presence of copulatory plugs was determined and sperm motility, morphology, and number were assessed.
Result	:	The fertility index (number of pairs producing litters divided by the number of pairs cohabitated, X 100) was not affected by exposure to TCP. However, the number of litters per pair decreased in a dose related manner, and the proportion of pups born live in the high dose group was significantly lower than the control. In the crossover mating pahse, impaired fertility was found in both male and female mice treated with 0.2% TCP, with greater effect in the females. The high dose group also demonstrated significantly lower body weights and changes in adrenal morphology. An examination of sperm from the F1 males at necropsy found normal sperm concentration and morphology in all dose groups. Sperm motility was significantly decreased in the 0.05% and 0.1% males (0.2% males not examined for sperm motility). TCP impaired fertility in both sexes of mice and adversely affected sperm motility even at the lowest dose.
Reliability	:	(2) valid with restrictions

20.06.2001 (5)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.10 OTHER RELEVANT INFORMATION

Type	:	Metabolism
Method	:	The absorption, distribution, metabolism, and elimination of a single dose of tri-ortho-cresyl phosphate (TOCP, the ortho isomer of TCP) was evaluated in adult White Leghorn hens. Uniformly ring labeled 14C-TOCP was administered at a dose of 50 mg in a capsule to each of twelve hens which were then housed in metabolism cages. Excreta was collected daily for up to 5 days. Three control hens were included in the study. Blood was collected via heart puncture just prior to sacrifice. Three treated hens were terminated at 0.5, 1, 2, and 5 days after receiving TOCP. Tissue distribution of the radioactivity was determined in all of the animals. TOCP and metabolites were extracted with ethyl acetate and identified using HPLC and reference standards.
Result	:	Hens that received the 50 mg doses did not express either acute cholinergic signs or symptoms of delayed neurotoxicity. TOCP was absorbed from the gastrointestinal tract, with the highest concentrations appearing in the bile, kidneys, liver, and lungs. About 47% of the

radioactivity was excreted in the first 12 hours. About 99% was eliminated after 5 days. HPLC identified TOCP and nine metabolites. The active metabolite, saligenin cyclic-o-cresyl phosphate, was the predominent compound found in the excreta. The relatively slow excretion of TOCP and its metabolites by the hen may contribute to its sensitivity as an animal model in the study of delayed neuropathy.

Reliability : (1) valid without restriction
19.07.2001 (2)

Type : Metabolism
Method : The disposition of 10 daily doses of 14C-tri-ortho-cresyl phosphate (14C-TOCP), 50 mg/kg, was determined in male Fischer 344 rats. Groups of 3 rats each were sacrificed at 24, 48, 72, and 96 hours after the last dose. The distribution of radioactivity in 19 tissues was measured. Urine and feces were collected up until the time of sacrifice. TOCP and its metabolites were analyzed and quantified by HPLC using appropriate reference standards.
Result : The highest concentrations of radioactivity were found in the liver, adipose tissue, epididymis, sciatic nerve, plasma, and erythrocytes. The lowest concentrations were in the testes, brain, spleen, and heart. All of the administered radioactivity had been excreted 4 days after the last dose. Analysis of the radioactivity in several tissues showed TOCP to be the predominent compound present. The major metabolites were identified.
Reliability : (2) valid with restrictions
19.07.2001 (26)

Type : Neurotoxicity
Remark : In one of the earliest articles on phosphate ester neurotoxicity, Henschler describes "tricresyl phosphate poisoning" as related to peripheral neurotoxicity. He identifies the ortho isomer of tricresyl phosphate as the neurotoxic component and describes the degenerative changes that occur to peripheral nerves in response to different amounts of the ortho isomer present in tricresyl phosphate. This article also reviews may of the earlier publications related to accidental exposure to tricresyl phosphate, including the "polyneuritis" occurring as a result of TOCP ingestion during the depression. Early animal studies are also reviewed.
Reliability : (2) valid with restrictions
27.07.2001 (15)

Type : Neurotoxicity
Remark : Bischoff reviews the neurotoxicity of tri-ortho-cresyl phosphate (TOCP) and provides pictures of neurological changes resulting from exposure to TOCP. He provides a detailed description of the histological changes that occur, the time of occurrence the specific changes post-exposure, and the use of the adult hen as a sensitive animal model in which to evaluate the neurotoxic potential of phosphate esters.
27.07.2001 (3)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

Memo : Allergic Contact Dermatitis
Method : Two women and 2 men were referred to the Oregon Health Sciences University Dermatitis Clinic because of clinical dermal reactions suggestive of allergic contact dermatitis. All four patients were exposed to Band-Aid brand adhesive bandages. Two of the patients were patch tested with Babd-Aid Strips and with several components of the strip. Tricresyl phosphate (TCP), which is used as the plasticizer in the vinyl backing, was not tested in the two patients. Patch test reactions were evaluated at 2 and 7 days.
Result : One of the two patients had a strong positive reaction to Band-Aid Brand

Sheer Strips and to the antioxidant used in the strip, 2,5-di(tertiaryamyl) hydroquinone. While the article lists TCP as an ingredient in the Band-Aid plastic, TCP was not tested as a potential allergan in the two patients in this study. The article mentions that TCP caused allergic contact dermatitis in previous studies.

Reliability : (4) not assignable
20.06.2001

(25)

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(4) Carlton, B. D., Basaran, A. H., Mezza, L. and Smith, M. K. Examination of the reproductive effects of tricresyl phosphate administered to Long-Evans rats. Toxicology 46:321-328, 1987.

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7.1 END POINT SUMMARY

7.2 HAZARD SUMMARY

7.3 RISK ASSESSMENT